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SYNTHESES IN THE EPINEPHRINE SERIES

PART II.

BY

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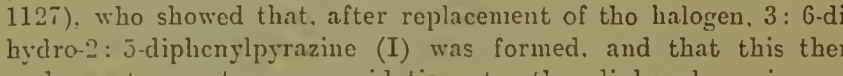
CCLVII.—*Syntheses in the Epinephrine Series. Part II. The Formation and Properties of Some 2 : 5- and 2 : 6-Substituted Pyrazines and their Conversion into Amino-ketones and Imino-diketones.*

By Frank Tutin.

In a recent communication (Tutin, Caton, and Hann, Trans., 1909, **95**, 2113) it was shown that the action of ammonia on ω-chloro-*p*-hydroxyacetophenone did not result in the formation of ω-amino-*p*-hydroxyacetophenone, but yielded only resinous products. This result was considered somewhat remarkable, inasmuch as the analogous chloro-*mp*-dihydroxy-ketone readily yields the corresponding amine (D.R.-P. 155632). The behaviour of a number of

ω-chloroacetophenono derivatives on heating with ammonia has therefore been investigated, with the result that it has been rendered evident that these compounds may be divided into three classes, according to the products which they yield on this treatment. Thus, ω-chloro-*mp*-dihydroxyacetophenone, on treatment with ammonia, behaves in a normal manner, yielding the corresponding amine. Only amorphous products result from the interaction of ammonia and ω-chloro-*p*-hydroxyacetophenone, *ω-chloro*-o-*methoxyacetophenone*, or *ω-chloro*-op-*dimethoxyacetophenone*. When, however, either ω-chloroacetophenone, ω-chloro-*p*-methoxyacetophenone, or *ω-chloro*-mp-*dimethoxyacetophenone* is heated with alcoholic ammonia, the principal product of the reaction is a mixture of 2:5- and 2:6-substituted pyrazines, in about equal proportions.

The formation of 2:5-diphenylpyrazino (II) from ω-bromoacetophenone and ammonia was studied by Gabriel (*Ber.*, 1908, **41**, 1127), who showed that, after replacement of tho halogen, 3:6-dihydro-2:5-diphenylpyrazine (I) was formed, and that this then underwent spontaneous oxidation to the diphenylpyrazine, as follows:



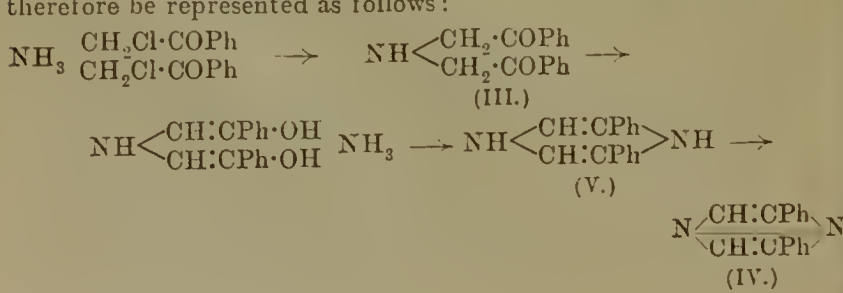
(I.) (II.)

The last-mentioned author, however, overlooked the fact that 2:6-diphenylpyrazino is also formed in this reaction, and the mode of production of this compound therefore remains to be explained. Gabriel (*loc. cit.*), however, identified diphenacylamine,

$$(Ph\cdot CO\cdot CH_2)_2NH,$$

as a product of tho interaction of ω-bromoacetophenone and ammonia, and tho present author has similarly obtained this base, as a minor product, from ω-chloroacetophenone.

It is now shown that diphenacylamine (III) and its derivatives are intermediate compounds in the formation of 2:6-substituted pyrazines, for they pass into the latter on heating with ammonia. The series of changes which results in the formation of 2:6-diphenylpyrazine (IV) from ω-chloroacetophenone and ammonia may therefore be represented as follows:



(III.) (V.) (IV.)

According to this scheme the action of ammonia on diphenacylamine first results in the production of 1 : 4-*dihydro*-2 : 6-*diphenylpyrazine* (V), which then passes into 2 : 6-diphenylpyrazine by spontaneous oxidation. The change might, however, conceivably take place as follows:

$$NH{<}\begin{matrix}CH_2\cdot COPh\\ CH_2\cdot COPh\end{matrix}\ NH_3 \longrightarrow NH{<}\begin{matrix}CH_2\cdot CPh{:}NH\\ CH{:}CPh\cdot OH\end{matrix} \longrightarrow$$

$$NH{<}\begin{matrix}CH_2\cdot CPh\\ CH{=}CPh\end{matrix}{>}N \longrightarrow N{<}\begin{matrix}CH{:}CPh\\ CH{:}CPh\end{matrix}{>}N.$$

(VI.)

If this be the case, the intermediate compound will be 3 : 4-*dihydro*-2 : 6-*diphenylpyrazine* (VI).

The change which is here shown to occur on heating compounds of the type $(R\cdot CO\cdot CH_2)_2NH$ with ammonia does not appear to have been observed before, and it therefore seems to afford a new, general method for the production of 2 : 6-substituted pyrazines.

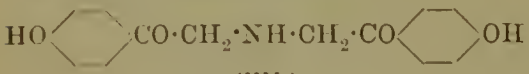
The interaction of ammonia and ω-chloro-*p*-methoxyacetophenone proceeds similarly to that of ω-chloroacetophenone and ammonia, yielding, as principal products, pp′-*dimethoxy*-2 : 5-*diphenylpyrazine* (m. p. 223°) and pp′-*dimethoxy*-2 : 6-*diphenylpyrazine* (m. p. 137·5°). The former of these two compounds is of particular interest, as, on fusion, it passes into the "liquid-crystalline" state, and this phase persists over an exceptionally large range of temperature, namely, 41·4°. *pp′*-Dimethoxy-2 : 5-diphenylpyrazine therefore represents a new addition to the already considerable list of "liquid-crystalline" *p*-anisyl derivatives, but it appears to be the first compound of this class in which the anisyl group is attached to a ring. A further interesting property of *pp′*-dimethoxy-2 : 5-diphenylpyrazine is that its solutions exhibit a violet-blue fluorescence, a behaviour which has not previously been observed amongst pyrazine derivatives. Furthermore, on the addition of a drop of concentrated hydrochloric or sulphuric acid to a chloroform solution of this base, a most brilliant green fluorescence is produced. *pp′*-Dimethoxy-2 : 6-diphenylpyrazine behaves in marked contrast to its 2 : 5-substituted isomeride, as it fluoresces but slightly, and only in neutral solution, and it does not pass into the "liquid-crystalline" state.

ω-*Chloro*-mp-*dimethoxyacetophenone* yielded mm′pp′-*tetramethoxy*-2 : 5-*diphenylpyrazine* (m. p. 208°) and mm′pp′-*tetramethoxy*-2 : 6-*diphenylpyrazine* (m. p. 160°) on treatment with ammonia, neither of which passes into the "liquid-crystalline" state. The former compound is, however, strongly fluorescent, but only in neutral solution.

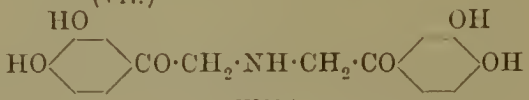
It is furthermore shown in the present communication that the series of changes which result respectively in the formation of

2:5-substituted pyrazines from ω-aminoacetophenone or its derivatives, and in the conversion of diphenacylamine or its derivatives into 2:6-substituted pyrazines, may be reversed by means of hydriodic acid. Thus, when 2:5-diphenylpyrazine is heated with hydriodic acid, reduction followed by hydrolysis occurs, resulting in the formation of two molecules of ω-aminoacetophenone hydriodide. Similarly, 2:6-diphenylpyrazine, when analogously treated, is converted into *diphenacylamine hydriodide* and ammonium iodide. Of course, when employing the pyrazine derivatives containing methoxyl groups, the methyl group is also eliminated by the hydriodic acid. This reaction therefore has afforded a new method of preparing ω-amino-*p*-hydroxyacetophenone and ω-amino-*mp*-dihydroxyacetophenone, two bases which are of interest on account of their physiological activity. The former of these bases was previously prepared by the present author in conjunction with Messrs. Caton and Hann (*loc. cit.*) from ω-chloro-*p*-acetoxyacetophenone, whilst the latter base is of special importance on account of its near relationship to epinephrine.

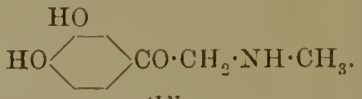
pp′-*Dihydroxydiphenacylamine* and mm′pp′-*tetrahydroxydiphenacylamine* have been prepared by the action of hydriodic acid on the previously-mentioned methoxy-2:6-diphenylpyrazines. It will readily be seen from a comparison of the formulæ given below that *pp*′-dihydroxydiphenacylamine (VII) and, especially, *mm*′*pp*′-tetrahydroxydiphenacylamine (VIII) are closely related to the ketone derived from epinephrine (IX), as also to the above-mentioned two ω-aminohydroxyacetophenones:



(VII.)



(VIII.)

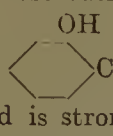


(IX.)

It was therefore to be expected that these two diphenacylamine derivatives would be possessed of physiological activity, and their properties have accordingly been investigated in the Wellcome Physiological Research Laboratories by Dr. H. H. Dale, to whom the author is indebted for the following and the subsequently mentioned physiological experiments. It was found that each of these compounds, in the form of salts, when injected intravenously into cats, caused a rise in blood-pressure, *pp*′-dihydroxydiphenacyl-

amine (VII) having an action similar to that of the related compound, ω-amino-*p*-hydroxyacetophenone (Tutin, Caton, and Hann, *loc. cit.*), whilst the corresponding tetrahydroxy-base (VIII) had a greater activity, more resembling that of the ketone derived from epinephrine (IX).

It has already been mentioned that ω-chloro-*o*-methoxyacetophenone and ω-chloro-*op*-dimethoxyacetophenone yield only amorphous products when heated with ammonia, whereas the analogous compounds containing the methoxyl groups in the *m*- and *p*-positions readily yield substituted pyrazines. It therefore appears that the presence of a methoxyl group in the *o*-position with respect to the side-chain precludes the formation of pyrazines from ω-chloroacetophenone derivatives, although the reason for this is not apparent.

On account of the above-mentioned property of the *o*-substituted ω-chloroacetophenone derivatives here described, it was impossible to obtain from them the corresponding ω-aminohydroxyacetophenones in the way which has already been noted in connexion with the preparation of ω-amino-*p*-hydroxyacetophenone from ω-chloro-*p*-methoxyacetophenone. Recourse was therefore had to the use of potassium phthalimide, and by this means derivatives and salts of *ω-amino-o-hydroxyacetophenone* and *ω-amino-op-dihydroxyacetophenone* have been obtained. When examined physiologically, the *hydriodide* of the *o*-hydroxy-base was found to be practically inactive, whilst the corresponding salt of the *op*-dihydroxy-base had no greater activity than the analogous *p*-hydroxy-compound. It is therefore seen that hydroxyl groups in the *o*-position with respect to the side-chain are devoid of physiological activity in the class of compounds under consideration, a result which is in harmony with a previous observation of Dr. Dale, who found *o*-hydroxy-β-phenylethylamine,  , to be inert, whilst the analogous *p*-compound is strongly active (Barger, Trans., 1909, **95**, 1123).

ω-Chloro-*o*-methoxyacetophenone is formed, together with the corresponding *p*-compound, by the action of aluminium chloride on chloroacetyl chloride and anisole. The further action of aluminium chloride on ω-chloro-*o*-methoxyacetophenone results in the formation of *ω-chloro-o-hydroxyacetophenone*. The latter substance differs from the corresponding *p*-compound, inasmuch as it is quite insoluble in aqueous sodium carbonate, thus showing how the relative positions of the groups in the benzene nucleus affect the acidity of the hydroxyl group.

The above-mentioned substituted ω-aminoacetophenones, containing a hydroxyl group in the *o*-position with respect to the side-chain,

differ markedly in their properties from the previously-mentioned analogous compounds which are substituted in the *m*- or *p*-position, inasmuch as they condenso and oxidise, when dissolved in neutral solvents, to form 2:5-substituted pyrazines. oo′-*Dihydroxy*-2:5-*diphenylpyrazine* and oo′pp′-*tetrahydroxy*-2:5-*diphenylpyrazine* have thus been prepared.

The two *o*-substituted ω-aminoacetophenones described also show a singular behaviour when benzoylated, either by the Schotten-Baumann method or in pyridine solution, for, when thus treated, they yield benzoyl derivatives of internal anhydrides. It would appear possible that these condensation products are 1-*benzoylindoxyl* and 6-*benzoyloxy*-1-*benzoylindoxyl* respectively.

Gabriel (*loc. cit.*), from his work on ω-aminoacetophenone, concluded that α-amino-ketones of this type were incapable of existence in the free state, but always underwent condensation when liberated from their salts. It is evident, however, from the results given in the present paper that this is not invariably the case. Thus, ω-aminoacetophenone, ω-amino-*p*-methoxyacetophenone, ω-amino-*mp*-dimethoxyacetophenone, and ω-amino-*o*-hydroxyacetophenone condense spontaneously, yielding pyrazine derivatives in the manner shown by Gabriel. ω-Amino-*p*-hydroxyacetophenono and ω-amino-*mp*-dihydroxyacetophenone, on the other hand, cannot be caused to condense; whilst ω-amino-*op*-dihydroxyacetophenone possesses properties between those of these two groups, for it can be obtained in the free state, although it condenses somewhat readily.

Experimental.

Interaction of ω-Chloroacetophenone and Ammonia.

Chloroacetyl chloride was dissolved in an excess of benzene, and one molecular proportion of aluminium chloride added. A violent reaction ensued, and, when this had subsided, ice and hydrochloric acid were added. The aqueous layer was then separated, and, after washing the benzene solution with water, the greater part of the solvent was removed from it. On adding light petroleum to the concentrated liquid thus obtained, ω-chloroacetophenone separated in glistening plates, melting at 59°. The yield was nearly quantitative.

Fifteen grams of ω-chloroacetophenone were heated for one and a-half hours at 100° in sealed tubes with an excess of alcoholic ammonia. After allowing the contents of the tubes to cool, the solid which had separated was collected, washed with alcohol, and then extracted repeatedly with boiling xylene. The material undissolved by this treatment consisted entirely of ammonium chloride, but on concentrating the xylene extracts, a compound

separated in plates, melting at 194°. As thus obtained, this substance possessed a dark bluish-green colour, and was only obtained colourless after being treated, in acetic acid solution, with a small amount of potassium permanganate dissolved in the same solvent. When crystallised from xylene after this treatment, it formed large, colourless plates, melting at 194°, and was identified as 2 : 5-diphenylpyraziue (Found, C = 79·5; H = 5·1. Calc., C = 79·3; H = 5·0 per cent.)

This compound was first prepared by Staedel and Rügheimer (*Ber.*, 1876, **9**, 563), who described it under the name of "*iso*indol." As subsequently obtained by Staedel and Kleinschmidt (*ibid.*, 1880, **13**, 836), it was observed to exhibit diverse colours, and they regarded it as being "idiochromatic." Pure 2 : 5-diphenylpyrazine is, however, quite colourless, as has been shown by Gabriel (*Ber.*, 1908, **41**, 1127), who prepared it by the interaction of ω-bromoacetophenone and ammonia.

The original alcoholic filtrate from the 2 : 5-diphenylpyrazine and ammonium chloride was evaporated to a low bulk and largely diluted with benzene. The filtered liquid was then again evaporated as far as possible, and the residue dissolved in alcoholic hydrogen chloride, when the mixture rapidly became dark brown, but no blue colour was developed (see below). The solution was concentrated somewhat, and hot ethyl acetate added, when, on cooling the mixture, a crystalline substance separated in needles, which were collected and washed with a mixture of ethyl acetate and alcoholic hydrogen chloride. The product so obtained was dissolved in the minimum amount of absolute alcohol, and a little alcoholic hydrogen chloride added, when it immediately separated in soft, almost colourless needles, melting at about 189°:

0·2020 gave 0·1060 AgCl. Cl = 13·0.

$C_{16}H_{12}N_2,HCl$ requires Cl = 13·2 per cent.

This substance was identified as 2 : 6-*diphenylpyrazine monohydrochloride*,* since it yielded 2 : 6-diphenylpyrazine, which formed colourless needles, melting at 90°. (Found, C = 79·3; H = 5·2. Calc., C = 79·3; H = 5·0 per cent.)

2 : 6-Diphenylpyrazine monohydrochloride is almost insoluble in benzene or ethyl acetate, but it dissolves fairly readily in alcohol, owing to the fact that it becomes, for the most part, dissociated. It is not stable in moist air, and is instantly dissociated when brought in contact with water.

Gabriel (*loc. cit.*) did not note the formation of 2 : 6-diphenylpyrazine when he investigated the interaction of ω-bromoaceto-

* It has been found that the pyrazines are diacidic bases, and yield two series of salts (compare following paper).

phenone and ammonia, but it would appear certain that it must have been present in the reaction mixture examined by him.

The original filtrate from the 2 : 6-diphenylpyrazine hydrochloride was dark brown, and contained considerable resinous matter. It was largely diluted with water, filtered from the precipitated resin, concentrated somewhat, and treated with animal charcoal. On allowing the clear liquid to cool, a somewhat sparingly soluble compound separated, which melted at about 235°, and was subsequently identified as diphenacylamine hydrochloride, a compound which has been described by Gabriel (*loc. cit.*).

In a subsequent preparation of the above-described 2 : 5- and 2 : 6-diphenylpyrazines, a quantity (40 grams) of ω-chloroacetophenone was heated in an autoclave with an excess of alcoholic ammonia, the mixture being subsequently kept for fourteen days before it was worked up. After separating the ammonium chloride and 2 : 5-diphenylpyrazine in the manner already described, the residual solution containing the 2 : 6-base, which was of a much more pronounced red colour, and appeared to be freer from resinous matter than that obtained in the previous preparation, was mixed with a large volume of ether and extracted several times with a mixture of concentrated hydrochloric acid (1 part) and water (2 parts). This caused the separation of some brown, resinous matter, which was removed. The ethereal liquid was then evaporated, and the red residue dissolved in absolute alcohol, and a solution of hydrogen chloride in the same solvent added. The liquid then became deep blue, and, on cooling the mixture after adding some ethyl acetate, a solid separated, which, when collected, was seen to consist of a mixture of white and deep blue needles, the former predominating. The separation of these two products was tedious, but was eventually effected by taking advantage of the fact that the blue *hydrochloride* was somewhat more sparingly soluble in a boiling solution of hydrogen chloride in absolute alcohol than was the white one, which consisted of 2 : 6-diphenylpyrazine hydrochloride. The blue compound crystallised in small needles, which had no definite melting point, and were only stable in dry air or in an anhydrous solvent in the presence of a moderate excess of hydrogen chloride. The amount obtained was only about 0·5 gram, and consequently the formula could not be established :

0·3506 gave 0·4791 AgCl. Cl = 33·8 per cent.

The *base* obtained from this deep blue hydrochloride crystallised from alcohol in small tufts of brilliant scarlet crystals, melting at 195°. It was readily soluble in chloroform, ethyl acetate, or benzene, but only moderately so in alcohol. On exposing a solution of this scarlet-coloured base in chloroform or benzene to direct

sunlight, the colour was discharged in half-an-hour, a compound crystallising in yellow needles being formed.

Preparation of ω-Chloro-o- and -p-methoxyacetophenones.

ω-Chloro-*p*-methoxyacetophenone was prepared by Kunckell and Johannssen (*Ber.*, 1897, **30**, 1715; 1898, **31**, 170) by the interaction of anisole and chloroacetyl chloride in the presence of aluminium chloride. Mr. F. W. Caton, who conducted this operation for the present author, found it important to avoid the use of any excess of aluminium chloride and not to employ heat, as the methyl group is very easily eliminated. With the object of avoiding this hydrolysis, experiments were made with the use of sublimed ferric chloride, but the yield of condensed product so obtained was only small.

One molecular proportion of anisole was mixed with rather more than an equivalent amount of chloroacetyl chloride, and, after diluting the mixture with three times its volume of carbon disulphide, one molecular proportion of powdered aluminium chloride was cautiously added, the flask being kept cool during this operation. After three hours the carbon disulphide was decanted, the residue being decomposed with ice and hydrochloric acid and the product extracted with ether. The ethereal liquid was then shaken with aqueous sodium hydroxide, which removed small amounts of hydrolysed product and red resin, after which the solvent was evaporated. On fractionally crystallising the residue from alcohol, it was found to consist, for the most part, of ω-chloro-*p*-methoxyacetophenone (m. p. 102°), which formed long needles, but the more soluble fraction contained a second substance. This compound formed large, colourless, diamond-shaped plates, which, after being separated mechanically from the greater part of the *p*-compound and submitted to several recrystallisations, melted at 69°:

0·2154 gave 0·4571 CO_2 and 0·0993 H_2O. C = 57·9; H = 5·1.
0·2288 „ 0·1778 AgCl. Cl = 19·2.

$C_9H_9O_2Cl$ requires C = 58·5; H = 4·9; Cl = 19·2 per cent.

This substance was evidently *ω-chloro-o-methoxyacetophenone*, since it readily yielded salicylic acid on fusion with potassium hydroxide.

This appears to be the first time that the formation of an *o*-monosubstituted ketone by means of the Friedel and Crafts' reaction has been noted, although phenyl *o*-tolyl ketone has been stated to be formed by the interaction of toluene and benzoic acid in the presence of phosphoric oxide (Kollarits and Merz, *Ber.*, 1873, **6**, 538).

ω-Chloro-*o*-methoxyacetophenone is slightly volatile at the

ordinary temperature, and sublimes readily on heating. It is more volatile in steam than is the corresponding *p*-compound, and may be approximately separated from the latter by taking advantage of this property. When brought into contact with the skin, it causes considerable smarting, and it has an extremely irritant action on the eyes.

Attempts to prepare *o*-methoxydiphenylpyrazines by heating ω-chloro-*o*-methoxyacetophenone with alcoholic ammonia in sealed tubes resulted only in the formation of resinous products.

ω-Chloro-o-hydroxyacetophenone.

ω-Chloro-*o*-methoxyacetophenone was dissolved in carbon disulphide, one molecular proportion of powdered aluminium chloride added, and the mixture heated for two hours under a reflux condenser. The solvent was then removed, and the residue heated at 100° for ten minutes, after which ice and hydrochloric acid were added, and the product extracted with ether. On shaking the ethereal liquid with a solution of sodium carbonate, nothing was removed, but subsequent treatment with aqueous sodium hydroxide extracted a relatively small proportion of oily matter. The ethereal liquid, on evaporation, yielded a considerable quantity of unchanged ω-chloro-*o*-methoxyacetophenone, this compound being evidently much more stable towards aluminium chloride than is the corresponding *p*-derivative. The oil which had been removed by sodium hydroxide was dissolved in ether, and light petroleum added, which caused the separation of a viscid, red product, whereupon the mixture was shaken with animal charcoal, and filtered. After concentrating the filtrate, a substance separated in yellow, flattened needles, which, after recrystallisation from alcohol, melted at 101°:

0·1238 gave 0·2546 CO_2 and 0·0490 H_2O. C = 56·0; H = 4·4.

$C_8H_7O_2Cl$ requires C = 56·3; H = 4·3 per cent.

This substance was therefore *ω-chloro-o-hydroxyacetophenone*, $HO{\cdot}C_6H_4{\cdot}CO{\cdot}CH_2Cl$. It differed from the corresponding *p*-compound in being insoluble in aqueous sodium carbonate (comparo Tutin, Caton, and Hann, Trans., 1909, **95**, 2118).

*Interaction of ω-Chloro-*p*-methoxyacetophenone and Ammonia.*

ω-Chloro-*p*-methoxyacetophenone was heated in an autoclave for three hours at 110° with a large excess of alcoholic ammonia. When cool, the solid contained in the dark-coloured reaction mixture was collected and washed, first with alcohol, and subsequently with water. The residue was crystallised from xylene, when it separated in large leaflets, melting at 222°. The substance, as thus obtained,

could not be rendered colourless by recrystallisation, but different preparations of it exhibited diverse tints, such as dull green, purplish, or greenish-yellow. It was, however, rendered colourless by the means previously found useful in the case of 2 : 5-diphenylpyrazine (p. 2501), but the melting point was practically unchanged by this treatment. On crystallising the purified substance from glacial acetic acid or xylene, it formed large, colourless leaflets, but when crystallised from chloroform or ethyl acetate it separated in hexagonal plates :

0·1088 gave 0·2947 CO_2 and 0·0556 H_2O. C = 73·9 ; H = 5·7.
0·3246 ,, 29·0 c.c. N_2 (moist) at 20° and 728 mm. N = 9·8.
$C_{18}H_{16}O_2N_2$ requires C = 73·9 ; H = 5·5 ; N = 9·6 per cent.

A molecular-weight determination by the cryoscopic method gave the following result :

0·3153, in 33·2 of phenol, gave $\Delta t = -0·30°$. M.W. = 243.
$C_{18}H_{16}O_2N_2$ requires M.W. = 292.

Several attempts were made to estimate the number of methoxyl groups in this substance by Perkin's modification of Zeisel's method, but accurate results could not at first be obtained, owing to the great stability of the compound. It was eventually ascertained, however, that the methyl groups are rapidly eliminated if some glacial acetic acid be added to the hydriodic acid employed :

0·2096 gave 0·3366 AgI. OMe = 21·1.
$C_{16}H_{10}N_2(OMe)_2$ requires OMe = 21·2 per cent.

The compound was evidently *pp'-dimethoxy*-2 : 5-*diphenylpyrazine*, $C_4H_2N_2(C_6H_4·OMe)_2$, and its constitution was subsequently confirmed by its conversion by hydriodic acid into *ω-amino*-p-*hydroxyacetophenone hydriodide* and methyl iodide (p. 2520).

On heating *pp'*-dimethoxy-2 : 5-diphenylpyrazine, fusion occurs at 223°, and the substance passes into a "liquid-crystalline" state. This phase persists until a temperature of 265·4° is reached, when the "crystalline" liquid phase instantly passes into the normal liquid state. At the point of change it can easily be observed that the two liquid phases are immiscible, and the "liquid-crystalline" product appears to possess the greater density. The reverse change, from the normal liquid to the "liquid-crystalline" phase, occurs at precisely the same temperature, and is exhibited in a striking manner when viewed through crossed Nicol's prisms. The point of change from the "liquid-crystalline" to the normal liquid phase, and vice versa, of *pp'*-dimethoxy-2 : 5-diphenylpyrazine is a much more delicate criterion of the purity of this substance than is its melting point, as a mere trace of impurity causes a very appreciable lowering of the temperature of transition from one liquid phase

to the other, whilst an amount of extraneous substance sufficient to cause a depression of the melting point by about 3° completely extinguishes the "liquid-crystalline" phase.

pp'-Dimethoxy-2:5-diphenylpyrazine is practically insoluble in ether or alcohol, very sparingly soluble in chloroform, benzene, or ethyl acetate, moderately soluble in boiling xylene, and more readily so in glacial acetic acid. Its dilute solution in chloroform exhibits a violet-blue fluorescence, and when a drop of concentrated hydrochloric acid is added, a yellow colour is produced, accompanied by a most brilliant green fluorescence.

The original, dark-coloured, alcoholic filtrate from the ammonium chloride and *pp'*-dimethoxy-2:5-diphenylpyrazine was evaporated to dryness, the residue extracted with benzene, the solution evaporated, and the residue dissolved in absolute alcohol. A solution of hydrogen chloride in absolute alcohol was then added, when, after concentrating the solution, it was mixed with hot ethyl acetate. On cooling the mixture, a compound separated in yellow needles, which were collected, washed with a mixture of alcoholic hydrogen chloride and ethyl acetate, and recrystallised by dissolving them in absolute alcohol, adding alcoholic hydrogen chloride, concentrating the mixture, and then diluting it with ethyl acetate. Soft, yellow needles were thus obtained, which melted at about 178—180°:

0·2420 gave 0·1003 AgCl. Cl = 10·3.
$C_{18}H_{16}O_2N_2$,HCl requires Cl = 10·8 per cent.

This salt proved to be pp'-*dimethoxy*-2:6-*diphenylpyrazine monohydrochloride*, $C_4H_2N_2(C_6H_4\cdot OMe)_2$,HCl. It dissolves sparingly in ethyl acetate or chloroform containing an excess of hydrogen chloride, but is unstable in moist air, and is dissociated by alcohol or water.

pp'-*Dimethoxy*-2:6-*diphenylpyrazine*, $C_4H_2N_2(C_6H_4\cdot OMe)_2$, obtained from the above-described salt by treatment with water or alcohol, crystallised from the latter solvent in colourless needles, melting at 137·5°:

0·0987 gave 0·2670 CO_2 and 0·0505 H_2O. C = 73·8; H = 5·7.
$C_{18}H_{16}O_2N_2$ requires C = 73·9; H = 5·5 per cent.

pp'-Dimethoxy-2:6-diphenylpyrazine is very readily soluble in chloroform, ethyl acetate, benzene, or xylene, but only moderately so in alcohol. Its neutral solutions exhibit a slight blue fluorescence, but this is destroyed by the addition of concentrated hydrochloric acid. It does not pass into a "liquid-crystalline" state on fusion. The constitution of *pp'*-dimethoxy-2:6-diphenylpyrazine was subsequently proved by its conversion by means of hydriodic acid into

methyl iodide, ammonium iodide, and pp′-*dihydroxydiphenacylamine hydriodide* (p. 2522).

The filtrate from the crude *pp′*-dimethoxy-2:6-diphenylpyrazine hydrochloride was dark brown, and contained considerable resinous matter. It was digested with aqueous hydrochloric acid, filtered, and the filtrate treated with animal charcoal. After concentrating the liquid thus obtained, it deposited a relatively small amount of a sparingly soluble hydrochloride. This was recrystallised from water, when it formed leaflets, melting at 256°:

0·2459 gave 0·1003 AgCl. Cl = 10·0.

$C_{18}H_{19}O_4N,HCl$ requires Cl = 10·1 per cent.

This salt was doubtless pp′-*dimethoxydiphenacylamine hydrochloride*, $(MeO\cdot C_6H_4\cdot CO\cdot CH_2)_2NH,HCl$, as it was obtained in a manner analogous to that which resulted in the formation of diphenacylamine hydrochloride from ω-chloroacetophenone, and its properties are strictly analogous to those of the latter salt. Moreover, from evidence given in the latter part of this communication, it is evident that *pp′*-dimethoxydiphenacylamine must have been formed during the interaction of ammonia and ω-chloro-*p*-methoxyacetophenone, since the former base is an intermediate compound in the production of the above-described *pp′*-dimethoxy-2:6-diphenylpyrazine.

It has already been shown in connexion with the preparation of the 2:5- and 2:6-diphenylpyrazines that if the reaction mixture were kept for some time before it was worked up, a highly-coloured by-product was formed, together with these bases. This is also the case when working with the *p*-methoxy-derivatives, but in the latter instance several other compounds were also obtained in small amounts, possibly owing to the fact that the reaction mixture was examined much more fully than in the former case.

ω-Chloro-*p*-methoxyacetophenone was heated with alcoholic ammonia as above described, but the reaction mixture was kept for three weeks before being examined. The *pp′*-dimethoxy-2:5-diphenylpyrazine was isolated as before described, but with the use of chloroform instead of xylene. The mother liquors then yielded a small amount of a compound, which formed soft, colourless needles, melting at 232—233°. On working up the original filtrate from the *pp′*-dimethoxy-2:5-diphenylpyrazine and ammonium chloride in the manner previously described, a mixture of *pp′*-dimethoxy-2:6-diphenylpyrazine and another salt was obtained. The latter compound was evidently the *p*-methoxy-derivative of the blue hydrochloride previously described; it was dark green, and was separated from the salt of the pyrazine derivative in a manner analogous to that employed in connexion with the previously-

described blue compound. The mother liquors from these hydrochlorides yielded, together with traces of other compounds, a substance which formed yellow leaflets, melting at 213—214°, but did not fluoresce when treated in chloroform solution with hydrochloric acid. The deep green-coloured hydrochloride melted quite indefinitely, owing to dissociation, and this change was also readily brought about by treatment with any solvent which did not contain an excess of anhydrous hydrogen chloride. It yielded a deep crimson-coloured base, crystallising from alcohol in small, lustrous prisms, which were so dark red as to appear almost black, and melted at about 165°. This compound, like the corresponding phenyl derivative previously described, is decolorised by exposure to direct sunlight when dissolved, yielding a yellow substance, which formed needles (m. p. about 255°) from xylene. The amounts of these various by-products obtained was small, and their investigation was not further pursued.

Derivatives of ω-*Amino*-p-*methoxyacetophenone.*

It would appear that the above-described *pp'*-dimethoxy-2 : 5-diphenylpyrazine must have been formed by the condensation of two molecules of *ω-amino*-p-*methoxyacetophenone*, followed by spontaneous oxidation of the resulting pp'-*dimethoxy*-3 : 6-*dihydro*-2 : 5-*diphenylpyrazine* in a manner analogous to that which has been shown by Gabriel (*loc. cit.*) to result in the formation of 2 : 5-diphenylpyrazine from ω-aminoacetophenone. With the object, therefore, of verifying this conclusion, ω-amino-*p*-methoxyacetophenone was prepared, in the form of its hydrochloride, as follows.

ω-Chloro-*p*-methoxyacetophenone was heated for some time in a nickel crucible with rather more than one molecular proportion of potassium phthalimide. The reaction mixture was then extracted with boiling xylene, and the product which crystallised from this solvent after concentration was repeatedly boiled with large quantities of water for the removal of unchanged phthalimide. On recrystallising the residue from xylene, glistening leaflets, melting at 164—165°, were obtained:

0·1437 gave 0·3650 CO_2 and 0·0604 H_2O. C = 69·2; H = 4·6.

$C_{17}H_{13}O_4N$ requires C = 69·2; H = 4·4 per cent.

ω-*Phthalimino*-p-*methoxyacetophenone*,

$$MeO\cdot C_6H_4\cdot CO\cdot CH_2\cdot N\!<\!\begin{matrix}CO\\CO\end{matrix}\!>\!C_6H_4,$$

is very sparingly soluble in alcohol, ethyl acetate, or chloroform, but dissolves more readily in glacial acetic acid or boiling xylene.

The above-described phthalide derivative was boiled for eight hours with concentrated hydrochloric acid, when it gradually passed

into solution. The mixture was then deprived of phthalic acid by means of ether, and evaporated to dryness under diminished pressure. On crystallising the residue from alcohol, *ω-amino*-p-*methoxyacctophenone hydrochloride*,

$$MeO\cdot C_6H_4\cdot CO\cdot CH_2\cdot NH_2,HCl,$$

was obtained in small, colourless prisms, which melted and decomposed at 204°, after having become red:

0·2121 gave 0·1408 AgCl. Cl = 16·4.

$C_9H_{11}O_2N,HCl$ requires Cl = 16·6 per cent.

When an alkali is added to an aqueous solution of ω-amino-*p*-methoxyacetophenone hydrochloride, no immediate separation of base occurs. The mixture, however, rapidly darkens somewhat, and, after some time, a dark-coloured, semi-crystalline product separates. On purification, this yielded *pp'*-dimethoxy-2:5-diphenylpyrazine (m. p. 223°), thus proving that a change analogous to that observed by Gabriel (*loc. cit.*) had occurred.

ω-Amino-p-*mcthoxyacctophenone Platinichloride*,

$$(MeO\cdot C_6H_4\cdot CO\cdot CH_2\cdot NH_2)_2H_2PtCl_6.$$

—This derivative crystallised very readily in deep yellow leaflets, and melted and decomposed at 225—228°:

0·1434 gave 0·0373 Pt. Pt = 26·0.

$(C_9H_{11}O_2N)_2H_2PtCl_6$ requires Pt = 26·3 per cent.

ω-Amino-p-*mcthoxyacetophcnone Aurichloride*,

$$MeO\cdot C_6H_4\cdot CO\cdot CH_2\cdot NH_2,HAuCl_4.$$

—The *aurichloride* did not crystallise readily, but was eventually obtained in handsome, golden-coloured leaflets, which melted at 74°, and evidently contained water of crystallisation:

0·2024 gavo 0·0762 Au. Au = 37·6.

$C_9H_{11}O_2N,HAuCl_4,H_2O$ requires Au = 37·6 per cent.

ω-Amino-p-methoxyacetophenone picrate, $C_9H_{11}O_2N,C_6H_3O_7N_3$, formed small, bright yellow leaflets, which, like the preceding compound, contained water of crystallisation. It melted and decomposed at 185°.

The *mercurichloride* crystallised very readily in long, colourless needles, which melted at 171°.

ω-Chloro-mp-*dimethoxyacetophcnone.*

Catechol was methylated by means of methyl sulphate,* and the resulting veratrole purified by distillation. The veratrole was then

* Perkin and Weizmann (Trans., 1906, **89**, 1649) state that an almost quantitative yield of veratrole may be obtained by treating 100 grams of catechol with 75 grams of methyl sulphate and 150 grams of potassium hydroxide. The figures

dissolved in carbon disulphide, an equivalent amount of chloroacetyl chloride added, and then one molecular proportion of powdered aluminium chloride introduced. The mixture was heated on a water-bath for two hours, but the reaction which ensued was by no means violent. The carbon disulphide was then removed and the residue decomposed by ice and hydrochloric acid, the product being extracted with ether. On shaking the ethereal liquid with aqueous potassium hydroxide, a small quantity of demethylated product was removed. The ether was then evaporated, and the residue deprived of a fairly large proportion of unchanged veratrole by means of steam. The non-volatile product was crystallised from alcohol, when it yielded *ω-chloro*-mp-*dimethoxyacetophenone*, $(MeO)_2C_6H_3\cdot CO\cdot CH_2\cdot Cl$, which formed small, colourless prisms, melting at 101°:

0·1172 gave 0·2394 CO_2 and 0·0538 H_2O. C = 55·8; H = 5·1.

$C_{10}H_{11}O_3Cl$ requires C = 55·9; H = 5·1 per cent.

ω-Chloro-*mp*-dimethoxyacetophenone is moderately soluble in alcohol, but much more readily so in ethyl acetate or chloroform. When in the dry state, it occasions violent sneezing.

The Interaction of ω-Chloro-mp-*dimethoxyacetophenone and Ammonia.*

ω-Chloro-*mp*-dimethoxyacetophenone was heated in an autoclave for three hours at 110° with a large excess of absolute alcoholic ammonia. When cool, the solid contained in the reaction mixture was collected, washed with alcohol, and then extracted many times with boiling xylene. The xylene extracts, on cooling, deposited a dark red, crystalline powder, melting at 208°. After treatment with a small amount of potassium permanganate in glacial acetic acid solution, in the manner previously described, it separated from glacial acetic acid in light grey needles, which melted at the same temperature as before this treatment:

0·1130 gave 0·2834 CO_2 and 0·0590 H_2O. C = 68·4; H = 5·8.

$C_{20}H_{20}O_4N_2$ requires C = 68·2; H = 5·7 per cent.

This compound was evidently mm′pp′-*tetramethoxy*-2 : 5-*diphenylpyrazine*, $C_6H_4(OMe)_2\cdot C_4H_2N_2\cdot C_6H_3(OMe)_2$, and its constitution was subsequently confirmed by its conversion into *ω-amino*-mp-*dihydroxyacetophenone hydriodide* and methyl iodide by the action of hydriodic acid (p. 2520). It is insoluble, or nearly so, in all the usual solvents with the exception of glacial acetic acid and boiling xylene, and in the latter solvent it dissolves but sparingly. Its much greater

given are, however, obviously incorrect, since the amount of catechol mentioned would require theoretically 229 grams of methyl sulphate and 102 grams of the alkali.

solubility in glacial acetic acid than in any other liquid employed appeared to be due to salt formation, as the solution was orange-yellow, and it was subsequently found that the tetramethoxy-diphenylpyrazines are more strongly basic than the other compounds of this class described in the present communication. A very dilute solution of *mm'pp'*-tetramethoxy-2:5-diphenylpyrazine in chloroform exhibits a strong blue fluorescence, but this phenomenon disappears on the addition of a drop of concentrated hydrochloric acid, a non-fluorescent, deep yellow liquid being produced. On fusion, this pyrazine derivative does not pass into a "liquid-crystalline" state, as is the case with the corresponding *pp'*-dimethoxy-compound.

The original alcoholic filtrate from the *mm'pp'*-tetramethoxy-2:5-diphenylpyrazine and ammonium chloride was evaporated to dryness, the residue extracted with benzene, the solution again evaporated, and the product so obtained dissolved in a small amount of absolute alcohol and a solution of hydrogen chloride in the same solvent added. On cooling the dark brown mixture, a compound separated in deep yellow needles. This was collected, washed with alcoholic hydrogen chloride, and recrystallised from absolute alcohol by the addition of a solution of hydrogen chloride in this solvent, when long, deep yellow, soft needles were obtained, which melted at about 195—200°:

0·2030 gave 0·0730 AgCl. Cl = 8·9.

$C_{20}H_{20}O_4N_2,HCl$ requires Cl = 9·1 per cent.

This compound was mm'pp'-*tetramethoxy*-2:6-*diphenylpyrazine monohydrochloride*, $C_6H_3(OMe)_2{\cdot}C_4H_2N_2{\cdot}C_6H_3(OMe)_2,HCl$. It was readily dissociated by water, or by alcohol, unless the latter contained an excess of hydrogen chloride. It yielded mm'pp'-*tetramethoxy*-2:6-*diphenylpyrazine*, which, when crystallised from alcohol, formed long, almost colourless needles, melting at 160°:

0·1079 gave 0·2734 CO_2 and 0·0563 H_2O. C = 68·0; H = 5·8.

$C_{20}H_{20}O_4N_2$ requires C = 68·2; H = 5·7 per cent.

This base was rather sparingly soluble in alcohol, but readily so in benzene, xylene, chloroform, glacial acetic acid, or ethyl acetate, and differed from the corresponding 2:5-compound, inasmuch as its solutions exhibited no fluorescence. Its constitution was subsequently confirmed by its conversion into mm'pp'-*tetrahydroxydiphenacylamine hydriodide*, methyl iodide, and ammonium iodide by means of hydriodic acid (p. 2523).

ω-Chloro-op-*dimethoxyacetophenone.*

Resorcinol dimethyl ether was prepared from resorcinol by the action of methyl sulphate and potassium hydroxide, and purified by distillation. The dimethyl ether was then dissolved in carbon disulphide, and the requisite amount of chloroacetyl chloride added. One molecular proportion of powdered aluminium chloride was then introduced, when a violent reaction ensued. After removing the solvent, the residue was treated with ice and hydrochloric acid, the resulting solid being collected and crystallised from alcohol. A very good yield of small, colourless, prismatic needles, melting at 96°, was thus obtained:

0·1233 gave 0·2518 CO_2 and 0·0577 H_2O. C = 55·7; H = 5·2.

$C_{10}H_{11}O_3Cl$ requires C = 55·9; H = 5·1 per cent.

ω-Chloro-op-*dimethoxyacetophenone*, $(MeO)_2C_6H_3{\cdot}CO{\cdot}CH_2Cl$, is somewhat sparingly soluble in alcohol, but much more readily so in ethyl acetate or chloroform. It was formed in much better yield than the corresponding *mp*-compound.

Attempts to convert ω-chloro-*op*-dimethoxyacetophenone into pyrazine derivatives by heating with alcoholic ammonia resulted only in the formation of brown resins, just as was the case when ω-chloro-*o*-methoxyacetophenone was employed. It therefore appears that the presence of a methoxyl group in the ortho-position with respect to the side-chain precludes the formation of substituted pyrazines from ω-chloroacetophenone derivatives.

Attempts were made to prepare an ω-chlorotrimethoxyacetophenone by the interaction of chloroacetyl chloride and pyrogallol trimethyl ether, but without success.

ω-Amino-op-*dihydroxyacetophenone and its Derivatives.*

It is subsequently shown that the methoxy-2:5-diphenylpyrazines readily yield ω-aminohydroxyacetophenones, the formation of which was the primary object of this research. Since, however, no pyrazine derivative could be obtained from ω-chloro-*op*-dimethoxyacetophenone, other means had to be devised for the conversion of this compound into the desired dihydroxy-amine.

ω-Chloro-*op*-dimethoxyacetophenone was heated in a nickel crucible at about 160° with rather more than one molecular proportion of potassium phthalimide until the reaction mixture, which was at first fairly fluid, became almost solid. The product was then extracted several times with boiling xylene, and the combined filtered liquids concentrated to a small bulk. The product which separated on cooling was collected and repeatedly boiled with large

quantities of water until free from phthalimide, after which it was recrystallised from xylene or glacial acetic acid, when it formed acicular crystals, melting at 188°:

0·0903 gave 0·2209 CO_2 and 0·0394 H_2O. C = 66·7; H = 4·8.

$C_{18}H_{15}O_5N$ requires C = 66·5; H = 4·6 per cent.

ω-Phthalimino-op-*dimethoxyacetophenone*,

$$(MeO)_2C_6H_3\cdot CO\cdot CH_2\cdot N<\begin{matrix}CO\\CO\end{matrix}>C_6H_4,$$

is insoluble, or very sparingly soluble, in all the usual solvents, with the exception of glacial acetic acid and boiling xylene, in which it is moderately soluble.

The above-described phthalide derivative was boiled with concentrated hydriodic acid containing some glacial acetic acid, when it very gradually passed into solution. The mixture was then diluted with water, and repeatedly extracted with ether for the removal of the phthalic acid, after which it was evaporated to dryness under diminished pressure. The solid residue was then dissolved in alcohol, the solution concentrated, ethyl acetate added, and the mixture again evaporated somewhat, when *ω-amino*-op-*dihydroxyacetophenone hydriodide*, $C_6H_3(OH)_2\cdot CO\cdot CH_2\cdot NH_2,HI$, separated from the boiling mixture:

0·2196 gave 0·1733 AgI. I = 42·7.

0·4535 „ 0·3405 AgI. I = 42·8.

$C_8H_9O_3N,HI$ requires I = 43·0 per cent.

ω-Amino-*op*-dihydroxyacetophenone hydriodide forms nearly colourless needles, which decompose at 258°. It is readily soluble in water or alcohol, but dissolves only sparingly in ethyl acetate.

ω-Amino-op-*dihydroxyacetophenone Hydrochloride*,

$$C_6H_3(OH)_2\cdot CO\cdot CH_2\cdot NH_2,HCl.$$

—This salt was prepared by the addition of concentrated hydrochloric acid to an alcoholic solution of the corresponding hydriodide, when the new derivative immediately separated in needles. When crystallised from water or dilute alcohol, it yielded small, hard prisms, which melted at 280°, darkening previously:

0·3297 gave 0·2292 AgCl. Cl = 17·2.

$C_8H_9O_3N,HCl$ requires Cl = 17·4 per cent.

ω-Amino-op-*dihydroxyacetophenone Aurichloride*,

$$C_6H_3(OH)_2\cdot CO\cdot CH_2\cdot NH_2,HAuCl_4.$$

—The gold salt of ω-amino-*op*-dihydroxyacetophenone was readily soluble in water, but crystallised from its concentrated solution in orange-coloured leaflets, which, on heating, gradually darkened, and finally melted at 283°. The dried salt was analysed:

0·1201 gave 0·0467 Au. Au = 38·9.

$C_8H_9O_3N,HAuCl_4$ requires Au = 38·9 per cent.

ω-*Amino*-op-*dihydroxyacetophenone Platinichloride*, $[C_6H_3(OH)_2\cdot CO\cdot CH_2\cdot NH_2]_2,H_2PtCl_6$.

This derivative was rather readily soluble in water, and crystallised from this solvent in fawn-coloured needles, which melted and decomposed at 247°:

0·1037 gave 0·0294 Pt. Pt = 28·5.

$(C_8H_9O_3N)_2H_2PtCl_6$ requires Pt = 28·5 per cent.

ω-*Amino*-op-*dihydroxyacetophenone pierate*, $C_8H_9O_3N,C_6H_3O_7N_3$, crystallised from water in bright yellow needles, which melted and decomposed at 222°.

ω-*Amino*-op-*dihydroxyacetophenone*, $C_6H_3(OH)_2\cdot CO\cdot CH_2\cdot NH_2$, was prepared from the above-described hydriodide or hydrochloride by the addition of a hot concentrated solution of sodium carbonate to a similar solution of the respective salt, both liquids having previously been deprived of dissolved air by boiling. The new base then immediately separated in small, pink-coloured plates, which, on heating to 310°, suffered some decomposition, but did not melt:

0·1065 gave 0·2240 CO_2 and 0·0558 H_2O. C = 57·3; H = 5·8.

$C_8H_9O_3N$ requires C = 57·5; H = 5·4 per cent.

ω-Amino-*op*-dihydroxyacetophenone is soluble in both acids and alkali hydroxides, but is insoluble, or practically so, in all the usual solvents with the exception of pyridine, although when dissolved in the last-mentioned liquid it suffered change.

Attempts to prepare ω-*amino*-op-*dimethoxyacetophenone* by heating ω-phthalimino-*op*-dimethoxyacetophenone with hydrochloric acid were unsuccessful, as the methyl groups were partly eliminated by this treatment, the resulting product being a mixture.

oo′pp′-*Tetrahydroxy*-2 : 5-*diphenylpyrazine*.

ω-Amino-*op*-dihydroxyacetophenone was boiled with pyridine, when it slowly dissolved, the solution acquiring a yellow colour. The liquid was then concentrated and cooled, when a substance separated in yellow needles. This was collected, but when washed with ethyl acetate, or when dried, it lost pyridine of crystallisation, and became bright orange-coloured. It was unchanged at 326°, but at a higher temperature sublimed in yellow leaflets:

0·1033 gave 0·2447 CO_2 and 0·0400 H_2O. C = 64·6; H = 4·3.

$C_{16}H_{12}O_4N_2$ requires C = 64·8; H = 4·1 per cent.

This substance was evidently oo′pp′-*tetrahydroxy*-2 : 5-*diphenylpyrazine*, $C_6H_2(OH)_2\cdot C_4H_2N_2\cdot C_6H_3(OH)_2$, and had been formed by the condensation of two molecules of the original keto-base followed by spontaneous oxidation of the resulting oo′pp′-*tetrahydroxy*-

3 : 6-*dihydro*-2 : 5-*diphenylpyrazine*. It yielded unstable salts with the mineral acids, of which the *monosulphate* was bright orange and the *disulphate* intense purple. *oo'pp'*-Tetrahydroxy-2 : 5-diphenylpyrazine is very sparingly soluble in glacial acetic acid, more readily soluble in pyridine, and insoluble in all the other usual solvents.

oo'pp'-*Tetrabenzoyloxy*-2 : 5-*diphenylpyrazine*, $C_6H_3(OBz)_2 \cdot C_4H_2N_2 \cdot C_6H_3(OBz)_2$. —The above-described *oo'pp'*-tetrahydroxy-2 : 5-diphenylpyrazine readily underwent benzoylation when treated according to the Schotten-Baumann method, yielding a product which crystallised from ethyl acetate in glistening, colourless leaflets, melting at 212°:

0·0976 gave 0·2643 CO_2 and 0·0356 H_2O. C = 73·8; H = 4·0.

$C_{44}H_{28}O_8N_2$ requires C = 74·1; H = 3·9 per cent.

oo'pp'-*Tetrabenzoyloxy*-2 : 5-*diphenylpyrazine* is somewhat sparingly soluble in ethyl acetate and in alcohol, but dissolves readily in chloroform.

With the object of preparing the benzoyl derivative of ω-amino-*op*-dihydroxyacetophenone, the hydriodide of this base was dissolved in water, benzoyl chloride added, and then excess of aqueous potassium hydroxide introduced, and the mixture shaken for some time. The pasty product which separated was collected, dissolved in boiling absolute alcohol, and then submitted to steam distillation for the removal of the ethyl benzoate which had been formed from the occluded excess of benzoyl chloride. The non-volatile residue was dissolved in alcohol, when, on keeping, a crystalline benzoyl derivative separated, but by no means in quantitative yield. The mother liquors from this solid contained an uncrystallisable oil, which, from a subsequent observation, would appear to have been the compound which it was sought to prepare, namely, ω-*benzoylamino*-op-*dibenzoyloxyacetophenone*, $C_6H_3(OBz)_2 \cdot CO \cdot CH_2 \cdot NHBz$. The crystalline solid which was obtained formed small prisms, melting at 136—137°, and, on analysis, was found to be the benzoyl derivative of a condensation product of the base:*

0·1532 gave 0·4106 CO_2 and 0·0624 H_2O. C = 73·1; H = 4·5.

$C_{22}H_{15}O_4N$ requires C = 73·6; H = 4·2 per cent.

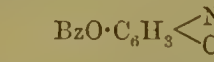
0·2970, in 24 of benzene, gave $\Delta t = -0·165°$. M.W. = 375.

$C_{22}H_{15}O_4N$ requires M.W. = 357.

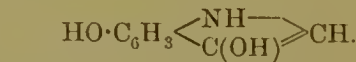
This *compound* was therefore the dibenzoyl derivative of an internal anhydride of ω-amino-*op*-dihydroxyacetophenone, and since an analogous compound was obtained from ω-amino-*o*-hydroxyacetophenone (p. 2518), but not from the related bases containing

* The same compound was obtained when ω-amino-*op*-dihydroxyacetophenone hydriodide was benzoylated in pyridine solution.

hydroxyl groups in the *m*- or *p*-positions, it would seem likely that the *o*-hydroxyl group was concerned in the anhydride formation. In view of this consideration, it would appear probable that the substance melting at 136—137° is a dibenzoyl derivative of 6-hydroxyindoxyl (X):



(X.)



(XI.)

6-Hydroxyindoxyl, however, might have been expected to react in its enolic form (XI), yielding a tribenzoyl derivative.

That one of the benzoyl groups was attached to nitrogen was proved by the conversion of this dibenzoyl derivative into ω-benzoylamino-*op*-dihydroxyacetophenone by the action of alkali hydroxides.

ω-*Benzoylamino*-op-*dihydroxyacetophenone*, $C_6H_3(OH)_2{\cdot}CO{\cdot}CH_2{\cdot}NHBz$. —A quantity of the dibenzoyl derivative melting at 136—137° was boiled with concentrated alcoholic potassium hydroxide for one hour, when water was added, and the mixture acidified with hydrochloric acid. A compound then separated in slender, glistening prisms, melting and decomposing at 260—265°:

0·1339 gave 0·3267 CO_2 and 0·0590 H_2O. C = 66·5; H = 4·8.

$C_{15}H_{13}O_4N$ requires C = 66·4; H = 4·8 per cent.

ω-*Benzoylamino*-op-*dihydroxyacetophenone* is very sparingly soluble in alcohol, ethyl acetate, chloroform, or benzene, moderately so in glacial acetic acid, and readily so in pyridine. On prolonged heating with concentrated hydrochloric acid, it yielded ω-amino-*op*-dihydroxyacetophenone hydrochloride and benzoic acid, and on benzoylation it yielded a compound which appeared to be the *tribenzoyl* derivative of the corresponding base. This compound was a liquid, and was doubtless identical with the similar product which was obtained together with the dibenzoyl derivative melting at 136—137°, as previously noted.

ω-*Phthalimino*-op-*dihydroxyacetophenone*.

During the hydrolysis of ω-phthalimino-*op*-dimethoxyacetophenone by means of hydriodic acid, it was observed that the reaction proceeded in two stages, the methyl groups being much more rapidly eliminated than was the phthalyl radicle. In one experiment, therefore, the reaction was stopped as soon as the evolution of methyl iodide had ceased, the mixture being diluted with water and cooled. A solid then separated, which was collected and washed. When recrystallised from acetic acid, this substance formed small tufts of short, colourless prisms, which gradually darkened above 250°, and fused at 270°:

0·1835 gave 0·4350 CO_2 and 0·0637 H_2O. C = 64·6; H = 3·8.
$C_{16}H_{11}O_5N$ requires C = 64·6; H = 3·7 per cent.

ω-Phthalimino-op-dihydroxyacetophenone,

$$C_6H_3(OH)_2\cdot CO\cdot CH_2\cdot N<\begin{matrix}CO\\CO\end{matrix}>C_6H_4,$$

is rather sparingly soluble in most solvents. When heated with concentrated hydrochloric or hydriodic acids, it yielded the corresponding amine.

ω-Phthalamino-op-dihydroxyacetophenone,

$$C_6H_3(OH)_2\cdot CO\cdot CH_2\cdot NH\cdot CO\cdot C_6H_4\cdot CO_2H.$$

—The above-described phthalimino-derivative was dissolved in aqueous potassium hydroxide, and the solution boiled for some time. The mixture was then acidified with hydrochloric acid, boiled with animal charcoal, and the filtered liquid concentrated to a small bulk and cooled. The solid which separated consisted largely of potassium chloride, but also contained crystals of an organic compound. The latter was isolated by extraction with boiling xylene, after which it was finally purified by crystallisation from water. Long, glistening leaflets were thus obtained, which melted at 227°:

0·1372 gave 0·3064 CO_2 and 0·0519 H_2O. C = 60·9; H = 4·2.
$C_{16}H_{13}O_6N$ requires C = 61·0; H = 4·1 per cent.

Derivatives of ω-Amino-o-hydroxyacetophenone.

Since ω-chloro-*o*-methoxyacetophenone gave only resinous products when heated with ammonia, it was necessary to employ potassium phthalimide for the conversion of this chloro-ketone into the corresponding amine, just as was the case with the analogous *op*-dimethoxy-compound (compare p. 2512).

ω-Chloro-*o*-methoxyacetophenone was therefore converted into the corresponding phthalimino-derivative in a manner precisely similar to that employed in the case of the *op*-dimethoxy-derivative. The resulting *ω-phthalimino-o-methoxyacetophenone*,

$$MeO\cdot C_6H_4\cdot CO\cdot CH_2\cdot N<\begin{matrix}CO\\CO\end{matrix}>C_6H_4,$$

was very sparingly soluble in most solvents, but was readily purified by crystallisation from slightly diluted acetic acid. It formed colourless, diamond-shaped plates, melting at 200·5°:

0·1553 gave 0·3972 CO_2 and 0·0632 H_2O. C = 69·5; H = 4·5.
$C_{17}H_{13}O_4N$ requires C = 69·2; H = 4·4 per cent.

This derivative was boiled for three hours with a mixture of glacial acetic acid and concentrated hydriodic acid. After freeing the liquid from phthalic acid by extraction with ether, the mixture was evaporated to dryness under diminished pressure, and the residue crystallised from a mixture of ethyl acetate and alcohol.

Very lustrous, colourless plates were thus obtained, which melted at 255°:

0·3846 gave 0·3230 AgI. I = 45·4.

$C_8H_9O_2N$,HI requires I = 45·5 per cent.

ω-Amino-o-hydroxyacetophenone hydriodide,

$HO{\cdot}C_6H_4{\cdot}CO{\cdot}CH_2{\cdot}NH_2$,HI,

is very readily soluble in water or alcohol, but only sparingly so in ethyl acetate. It does not tend to become discoloured, as is the case with salts of the analogous bases containing a hydroxyl group in the meta- or para-position with respect to the side-chain.

A quantity of this hydriodide was dissolved in pyridine and benzoylated by means of benzoyl chloride. The product crystallised readily from ethyl acetate, forming colourless plates, which melted at 133°:

0·1277 gave 0·3538 CO_2 and 0·0530 H_2O. C = 75·6; H = 4·6.

$C_{15}H_{11}O_2N$ requires C = 75·9; H = 4·7 per cent.

This compound was therefore evidently the benzoyl derivative of a condensation product of ω-amino-*o*-hydroxyacetophenone, and is doubtless constituted analogously to the corresponding derivative of the *op*-dihydroxy-base (p. 2516). It may therefore be 1-*benzoylindoxyl*, a compound which does not appear to have been prepared previously.

oo′-Dihydroxy-2: 5-*diphenylpyrazine*.

A quantity of ω-amino-*o*-hydroxyacetophenone hydriodide was dissolved in water and aqueous sodium carbonate added, the resulting precipitate being collected, and crystallised from xylene. A substance was thus obtained in yellow needles, which melted at 259—262°, and were insoluble in dilute acids. The same compound was obtained if the solution of the hydriodide were rendered alkaline by means of sodium hydroxide, and then acidified, the resulting precipitate being recrystallised from xylene:

0·0904 gave 0·2420 CO_2 and 0·0400 H_2O. C = 73·0; H = 4·9.

$C_{16}H_{12}O_2N_2$ requires C = 72·7; H = 4·5 per cent.

This substance was evidently a condensation product, and its properties indicated it to be *oo′-dihydroxy-2*: 5-*diphenylpyrazine*, $C_4H_2N_2(C_6H_4{\cdot}OH)_2$. It is very sparingly soluble or insoluble in nearly all solvents, and forms unstable salts of a bright red colour when treated with mineral acids in an anhydrous solvent. When heated above its melting point, it sublimed in yellow leaflets.

It appears from this result that ω-amino-*o*-hydroxyacetophenone, when dissolved, behaves in a manner strictly analogous to that exhibited by the *op*-dihydroxy-base. That is to say, that two molecules condense with the formation of *oo′-dihydroxy-3*: 6-*di-*

hydro-2: 5-*diphenylpyrazine*, which then undergoes spontaneous oxidation to the corresponding pyrazine derivative.

oo′-*Dibenzoyloxy*-2: 5-*diphenylpyrazine*, $C_4H_2N_2(C_6H_4\cdot OBz)_2$, was prepared by benzoylating the above-described pyrazine derivative in pyridine solution. It formed small, almost colourless prisms, which melted at 185°, but the amount available was not sufficient for analysis.

Action of Hydriodic Acid on pp′-*Dimethoxy*-2: 5-*diphenylpyrazine*.

As previously shown, the methoxy-2: 5-diphenylpyrazines described in the present paper, which contain the substituent ether groupings in the meta- and para-positions, are formed by the condensation of two molecules of an ω-aminomethoxyacetophenone, followed by spontaneous oxidation of the resulting dihydropyrazine derivative, as follows (Gabriel, *loc. cit.*):

$$NH_2\diagdown\begin{matrix}COR\cdot CH_2\\ CH_2\cdot COR\end{matrix}\diagup NH_2 \longrightarrow N\lessdot\begin{matrix}CR\cdot CH_2\\ CH_2\cdot CR\end{matrix}\gtrdot N \longrightarrow N\diagup\begin{matrix}CR{:}CH\\ CH{:}CR\end{matrix}\diagdown N.$$

The corresponding ω-aminohydroxyacetophenones, however, could not be caused to condense under any conditions.

This behaviour is the reverse of that shown by the ortho-substituted ω-aminoacetophenones, for ω-amino-*o*-methoxyacetophenone and ω-amino-*op*-dimethoxyacetophenone will not yield pyrazines, whilst the corresponding hydroxy-derivatives spontaneously pass into such compounds.

With the object therefore of preparing *pp′*-dihydroxy-2: 5-diphenylpyrazine, the action of hydriodic acid on *pp′*-dimethoxy-2: 5-diphenylpyrazine was investigated. It was found, however, that this acid alone had only an extremely slow action on the compound in question, but that if a quantity of acetic acid were added to the mixture, a change ensued with moderate rapidity. The product obtained, however, was not the expected hydroxydiphenylpyrazine, but the reaction proceeded further, fission of the pyrazine nucleus taking place, resulting in the formation of two molecules of ω-amino-*p*-hydroxyacetophenone (Tutin, Caton, and Hann, *loc. cit.*). It was thus shown that the series of reactions which result in the formation of pyrazine derivatives from ω-aminoacetophenones can be quantitatively reversed by means of hydriodic acid.

A quantity of *pp′*-dimethoxy-2: 5-diphenylpyrazine was boiled for two hours with a mixture of concentrated hydriodic and glacial acetic acids. The liquid was then diluted with water and extracted with ether for the removal of iodine, after which it was evaporated to dryness under diminished pressure. On crystallising the residue

from ethyl acetate, colourless, prismatic needles were obtained, which melted at 230°:

0·3435 gave 0·2885 AgI. I = 45·4.

$C_8H_9O_2N,HI$ requires I = 45·5 per cent.

ω-Amino-p-hydroxyacetophenone hydriodide,

$HO\cdot C_6H_4\cdot CO\cdot CH_2\cdot NH_2,HI$,

is much more soluble in organic solvents than is the corresponding hydrochloride (Tutin, Caton, and Hann, *loc. cit.*). On benzoylation, it yielded ω-benzoylamino-*p*-benzoyloxyacetophenone, melting at 173—174°.

Action of Hydriodic Acid on mm′pp′-*Tetramethoxy*-2 : 5-*diphenylpyrazine.*

mm′pp′-Tetramethoxy-2 : 5-diphenylpyrazine was boiled for two hours with a mixture of glacial acetic and concentrated hydriodic acids, after which the liquid was diluted, extracted with ether, and evaporated to dryness under diminished pressure. The residue was crystallised from a mixture of ethyl acetate and alcohol, when it formed small, nearly colourless prisms, melting at 247—248°:

0·2175 gave 0·1717 AgI. I = 42·7.

$C_8H_9O_3N,HI$ requires I = 43·0 per cent.

This salt was therefore evidently *ω-amino*-mp-*dihydroxyacetophenone hydriodide*, $C_6H_3(OH)_2\cdot CO\cdot CH_2\cdot NH_2,HI$. On rendering its solution alkaline with sodium carbonate, ω-amino-*mp*-dihydroxyacetophenone separated in nearly colourless leaflets, which gradually decomposed and melted above 235°. This base has previously been prepared by another method during the synthesis of epinephrine (D.R.-P. 155632), and the above-described reaction therefore affords a new means of obtaining this important compound.

Action of Hydriodic Acid on 2 : 6-*Diphenylpyrazine.*

As the action of hydriodic acid on the 2 : 5-substituted pyrazines was found to result in the complete disruption of the pyrazine ring, it was considered of interest to investigate the effect of this reagent on the analogous 2 : 6-substituted bases. It was then found that the nitrogen-containing ring was broken in this case also, in the following manner:

$$N\begin{matrix}CH{:}CR\\CH{:}CR\end{matrix}N \longrightarrow NH\begin{matrix}CH_2\cdot COR\\CH_2\cdot COR\end{matrix} + NH_3.$$

A quantity of 2 : 6-diphenylpyrazine was heated for several hours with a mixture of concentrated hydriodic and glacial acetic acids. On allowing the liquid to cool, a sparingly soluble hydriodide separated. This was collected, and recrystallised from glacial acetic

acid, when it formed flattened needles, which melted and decomposed at 211°. This salt proved to be *diphenacylamine hydriodide*, $(C_6H_5\cdot CO\cdot CH_2)_2NH,HI$:

0·1981 gave 0·1217 AgI. I = 33·2.

$C_{16}H_{15}O_2N,HI$ requires I = 33·3 per cent.

This hydriodide was converted into the corresponding hydrochloride by treatment with hydrochloric acid in alcoholic solution, when glistening leaflets were obtained, which melted at 235°, after previously becoming red. (Found, Cl = 12·4. Calc., Cl = 12·3 per cent.) This salt had all the properties of diphenacylamine hydrochloride, as described by Gabriel (*loc. cit.*), and it yielded gold and platinum salts, in agreement with the similar derivatives prepared by him.

The original acid filtrate from the diphenacylamine hydriodide was evaporated to dryness under diminished pressure, and the residue crystallised from a mixture of ethyl acetate and alcohol. A colourless salt was thus obtained, which dissolved easily in water, and was readily recognised by the usual tests as ammonium iodide.

Conversion of Diphenacylamine into 2 : 6-*Diphenylpyrazine.*

Both Gabriel (*loc. cit.*) and the present author (p. 2502) have obtained diphenacylamine by the interaction of ω-bromo- or chloroacetophenone and ammonia, and the present author has shown that 2 : 6-diphenylpyrazine is also formed in this reaction (p. 2501). Now, since diphenacylamine results when this pyrazine derivative is heated with hydriodic acid, it appeared to the present author that the former base might be the intermediate compound in the formation of the latter by the reaction mentioned. This has been found to be the case, for, when one of the above-described salts of diphenacylamine was heated with ammonia, 2 : 6-diphenylpyrazine was regenerated. It is thus seen that the change which results in the formation of 2 : 6-diphenylpyrazine is capable of reversion by means of hydriodic acid, just as has been shown to be the case with the analogous 2 : 5-substituted pyrazines.

A quantity of diphenacylamine hydrochloride was heated in a sealed tube for three hours at 100° with a large excess of a solution of ammonia in absolute alcohol. The reaction mixture was then evaporated to dryness, the residue extracted with benzene, and the benzene liquids evaporated. The dark-coloured residue so obtained was dissolved in a small amount of ethyl acetate, and a solution of hydrogen chloride in absolute alcohol added, when 2 : 6-diphenylpyrazine monohydrochloride (m. p. 189°) separated. On treatment with alcohol, this salt dissociated, yielding 2 : 6-diphenylpyrazine, melting at 90°.

It is, of course, evident that the interaction of diphenacylamine and ammonia must first result in the formation of a dihydro-2:6-diphenylpyrazine, the latter then undergoing spontaneous oxidation.

Action of Hydriodic Acid on pp′-*Dimethoxy*-2:6-*diphenylpyrazine.*

A quantity of *pp*′-dimethoxy-2:6-diphenylpyrazine was boiled for several hours with a mixture of concentrated hydriodic and glacial acetic acids. On allowing the mixture to cool, a very sparingly soluble hydriodide separated in long, colourless needles, which melted and decomposed at 251°:

0·1050 gave 0·1805 CO_2 and 0·0392 H_2O. C = 46·8; H = 4·1.

$C_{16}H_{15}O_4N,HI$ requires C = 46·5; H = 3·8 per cent.

This salt therefore was pp′-*dihydroxydiphenacylamine hydriodide*, $(HO\cdot C_6H_4\cdot CO\cdot CH_2)_2NH,HI$. It was very sparingly soluble in water, and rather more soluble in alcohol, but was insoluble in cold solvents in the presence of an excess of hydriodic acid. pp′-*Dihydroxydiphenacylamine*, prepared from this salt, formed dark red crystals, but as it was very unstable it was not further investigated.

pp′-*Dihydroxydiphenacylamine Hydrochloride*,

$(HO\cdot C_6H_4\cdot CO\cdot CH_2)_2NH,HCl$.

—This salt was prepared by the addition of concentrated hydrochloric acid to an alcoholic solution of the corresponding hydriodide. It crystallised from alcohol in colourless leaflets, or from water in needles, and melted at 279°. It is less soluble in alcohol than the hydriodide, but dissolves in water more readily than the latter:

0·2093 gave 0·0914 AgCl. Cl = 10·8.

$C_{16}H_{15}O_4N,HCl$ requires Cl = 11·0 per cent.

pp′-*Dihydroxydiphenacylamine Platinichloride*,

$[(HO\cdot C_6H_4\cdot CO\cdot CH_2)_2NH]_2H_2PtCl_6$.

—This derivative crystallised very readily in buff-coloured needles, which melted and decomposed at 230°:

0·1210 gave 0·0241 Pt. Pt = 19·9.

$(C_{16}H_{15}O_4N)_2H_2PtCl_6$ requires Pt = 19·9 per cent.

pp′-*Dihydroxydiphenacylamine Aurichloride*,

$(HO\cdot C_6H_4\cdot CO\cdot CH_2)_2NH,HAuCl_4$.

—This salt crystallised readily in bright yellow needles, which melted at 259° after undergoing some decomposition:

0·1012 gave 0·0319 Au. Au = 31·5.

$C_{16}H_{15}O_4N,HAuCl_4$ requires Au = 31·5 per cent.

pp′-*Dihydroxydiphenacylamine picrate*, $C_{16}H_{15}O_4N,C_6H_3O_7N_3$, forms long, bright yellow needles, which melt at 169°.

Conversion of pp′*-Dihydroxydiphenacylamine into* pp′*-Dihydroxy-2 : 6-diphenylpyrazine.*

pp′-Dihydroxydiphenacylamine hydrochloride was heated for two hours in a sealed tube at 100° with a large excess of a solution of ammonia in absolute alcohol. The mixture was then evaporated, and the residue extracted with boiling xylene. On crystallising from glacial acetic acid the material dissolved by the xylene, small, pale yellow prisms, melting at 305°, were obtained :

0·1210 gave 0·3192 CO_2 and 0·0496 H_2O. C = 72·5 ; H = 4·5.

$C_{16}H_{12}O_2N_2$ requires C = 72·7 ; H = 4·5 per cent.

This compound was evidently pp′*-dihydroxy-2 : 6-diphenylpyrazine*, $C_4H_2N_2(C_6H_4{\cdot}OH)_2$. It yielded unstable salts with the mineral acids, the *monohydrochloride* and *monosulphate* being orange-coloured, whilst the *disulphate* was deep reddish-purple.

Action of Hydriodic Acid on mm′pp′*-Tetramethoxy-2 : 6-diphenylpyrazine.*

mm′pp′-Tetramethoxy-2 : 6-diphenylpyrazine was heated with hydriodic acid in a manner similar to that described in connexion with the corresponding dimethoxy-compound. A hydriodide was thus obtained, which crystallised from acetic acid in colourless leaflets, and melted and decomposed at 236° :

0·1725 gave 0·0918 AgI. I = 28·3.

$C_{16}H_{15}O_6N$,HI requires I = 28·5 per cent.

mm′pp′*-Tetrahydroxydiphenacylamine hydriodide*,

$[C_6H_3(OH)_2{\cdot}CO{\cdot}CH_2]_2NH$,HI,

is somewhat more soluble in water than the corresponding dihydroxy-compound. On treating its aqueous solution with alkalis, a yellow colour is produced, but oxidation very rapidly ensues, with the development of a brown colour.

mm′pp′*-Tetrahydroxydiphenacylamine Hydrochloride*,

$[C_6H_3(OH)_2{\cdot}CO{\cdot}CH_2]_2NH$,HCl.

—This salt was prepared by the addition of concentrated hydrochloric acid to an alcoholic solution of the above-described hydriodide, when the new derivative immediately separated. It crystallises from water in colourless leaflets, which melt and decompose at 264° :

0·2687 gave 0·1075 AgCl. Cl = 9·9.

$C_{16}H_{15}O_6N$,HCl requires Cl = 10·0 per cent.

On treating a solution of mm′pp′*-tetrahydroxydiphenacylamine hydrochloride* with auric or platinic chloride, the respective metal was quickly deposited. A *mercurichloride* was obtained from the

hydrochloride in tufts of small, white needles, but it was unstable, and, on warming its solution, mercurous chloride soon separated.

mm′pp′-*Tetrahydroxydiphenacylamine picrate*,

$$[C_6H_3(OH)_2\cdot CO\cdot CH_2]_2NH,C_6H_3O_7N_3,$$

crystallised readily in tufts of yellow needles, which contained water of crystallisation, and, when air dried, melted at 112—115°.

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